PTO-1542
(4-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

9-566

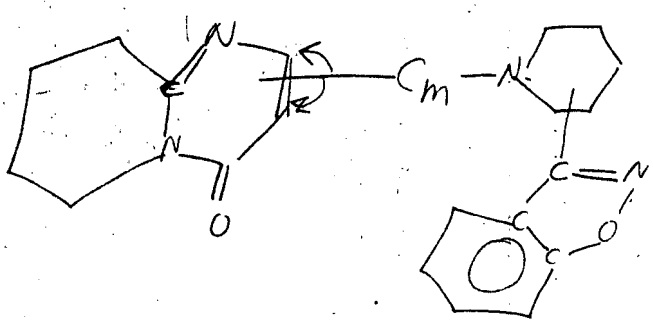
ONLINE SEARCH REQUEST FORM

USER Berch SERIAL NUMBER 932142

ART UNIT 1202 PHONE 4718 DATE 9-22-92

Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).



m = 1-3

MARY

STAFF USE ONLY

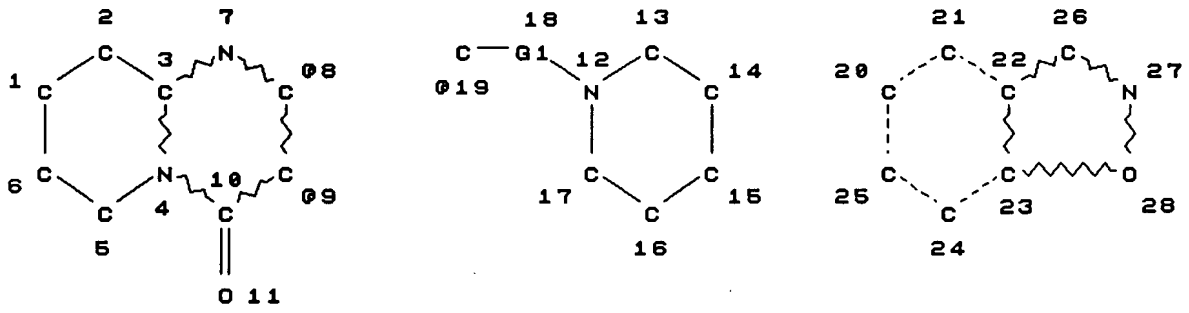
COMPLETED 9-23-92
SEARCHER BOB x4242
ONLINE TIME _____ TOTAL TIME _____
(in minutes)
NO. OF DATABASES _____

SYSTEMS
___ CAS ONLINE
___ DARC/QUESTEL
___ DIALOG
___ SDC
___ OTHER

=> fil reg; d stat que l3
FILE 'REGISTRY' ENTERED AT 15:43:21 ON 23 SEP 92
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1992 AMERICAN CHEMICAL SOCIETY (ACS)

STRUCTURE FILE UPDATES: 19 SEP 92 HIGHEST RN 143562-43-0
DICTIONARY FILE UPDATES: 22 SEP 92 HIGHEST RN 143562-43-0

L1 STR



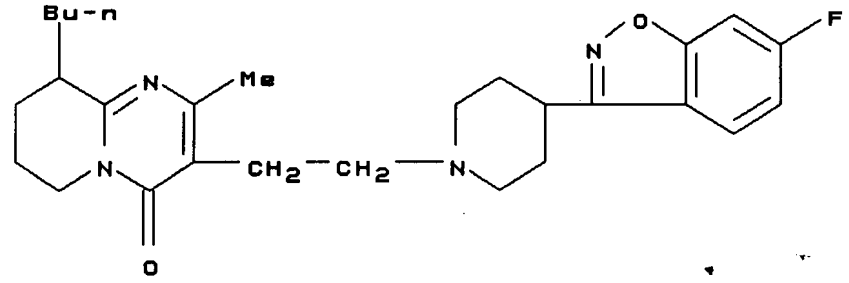
REP G1=(0-2) C
VPA 19-8/9 SE
NODE ATTRIBUTES: NONE

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 28
L3 18 SEA SSS FUL L1

100.0% PROCESSED 44 ITERATIONS 18 ANSWERS
SEARCH TIME: 00.00.05

=> d ide can l3 1-18

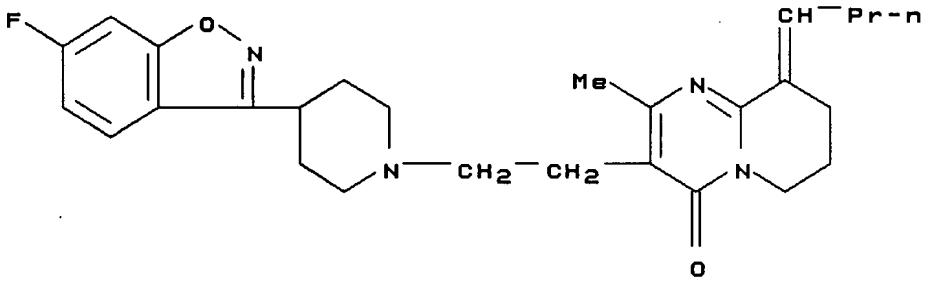
L3 ANSWER 1 OF 18 COPYRIGHT 1992 ACS
RN 138271-08-6 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 9-butyl-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-, (.+-.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C27 H35 F N4 O2
SR CA
LC CA
DES 3:(+-)



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

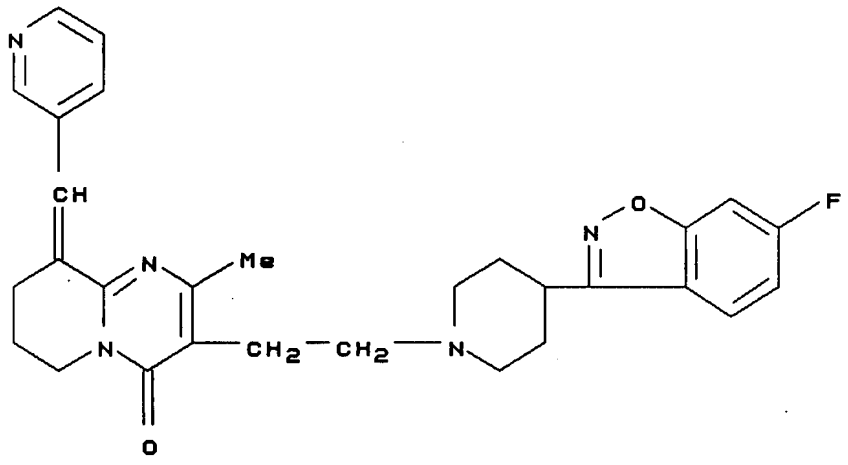
L3 ANSWER 2 OF 18 COPYRIGHT 1992 ACS
RN 138271-07-5 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 9-butylidene-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-, (E)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C27 H33 F N4 O2
SR CA
LC CA
DES 2:E



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

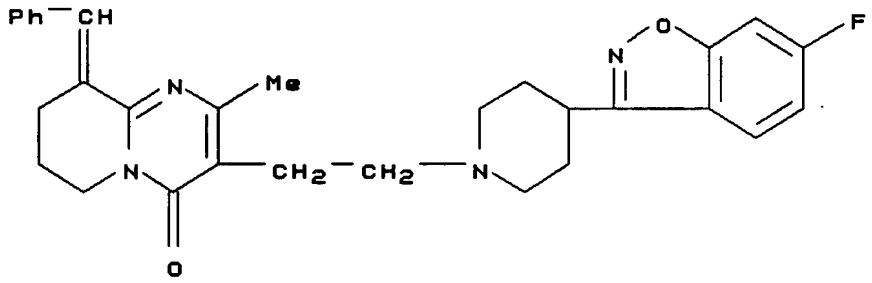
L3 ANSWER 3 OF 18 COPYRIGHT 1992 ACS
RN 138271-06-4 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-(3-pyridinylmethylene)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C29 H30 F N5 O2
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

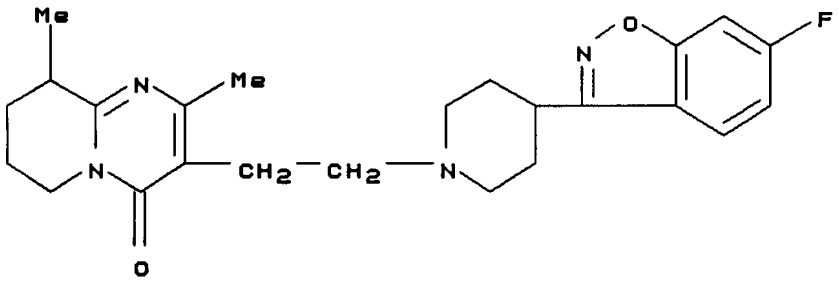
L3 ANSWER 6 OF 18 COPYRIGHT 1992 ACS
RN 138271-03-1 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-3-methyl-9-(phenylmethylene)-, (E)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C30 H31 F N4 O2
SR CA
LC CA
DES 2:E



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

L3 ANSWER 7 OF 18 COPYRIGHT 1992 ACS
RN 138271-01-9 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2,9-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C24 H29 F N4 O2
SR CA
LC CA

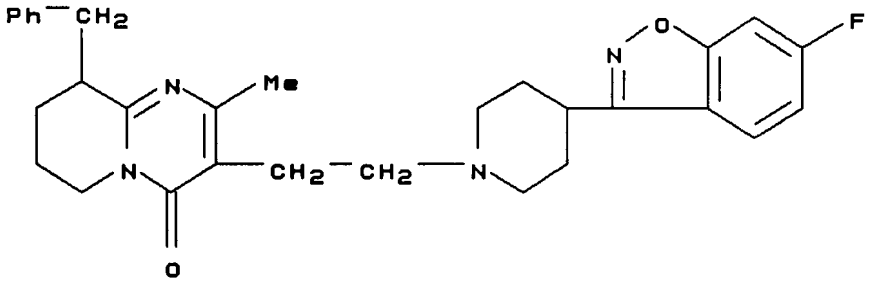


1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

L3 ANSWER 8 OF 18 COPYRIGHT 1992 ACS
RN 130049-90-0 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-7-hydroxy-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

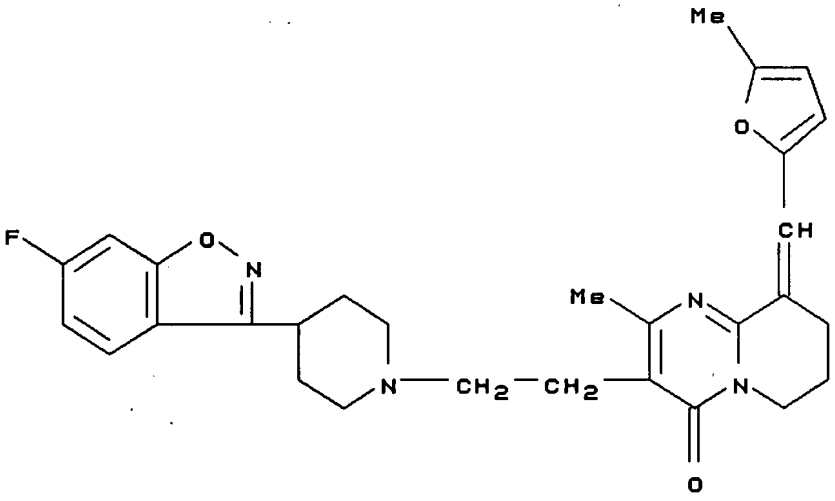
L3 ANSWER 4 OF 18 COPYRIGHT 1992 ACS
RN 138271-05-3 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-(phenylmethyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C30 H33 F N4 O2
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

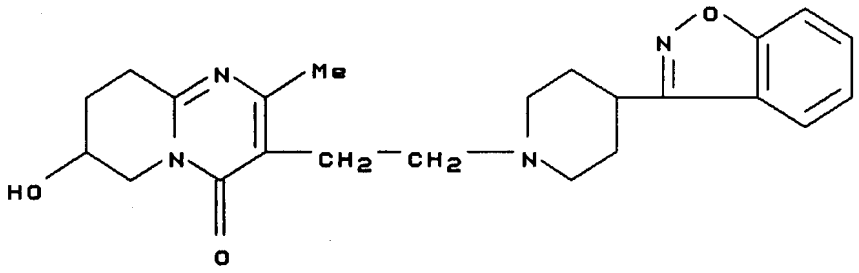
L3 ANSWER 5 OF 18 COPYRIGHT 1992 ACS
RN 138271-04-2 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-[(5-methyl-2-furanyl)methylene]-, (E)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C29 H31 F N4 O3
SR CA
LC CA
DES 2:E



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA116(5):41471m

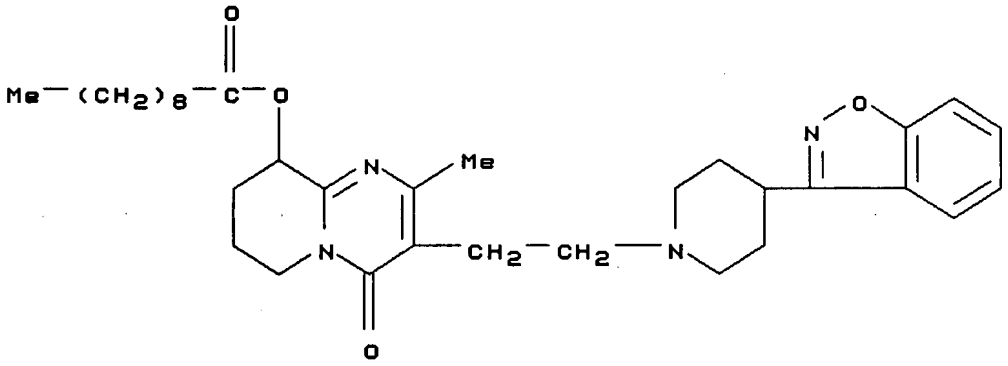
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C23 H28 N4 O3
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

L3 ANSWER 9 OF 18 COPYRIGHT 1992 ACS
RN 130049-89-7 REGISTRY
CN Decanoic acid, 3-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, decanoic acid deriv. (9CI)
CN 4H-Pyrido[1,2-a]pyrimidine, decanoic acid deriv. (9CI)
FS 3D CONCORD
MF C33 H46 N4 O4
SR CA
LC CA

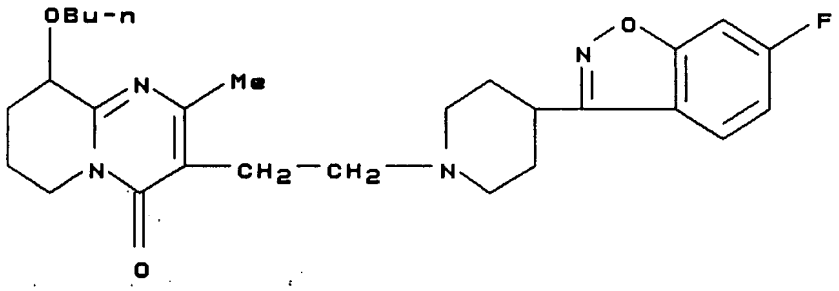


1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

L3 ANSWER 10 OF 18 COPYRIGHT 1992 ACS
RN 130049-88-6 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 9-butoxy-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C27 H35 F N4 O3

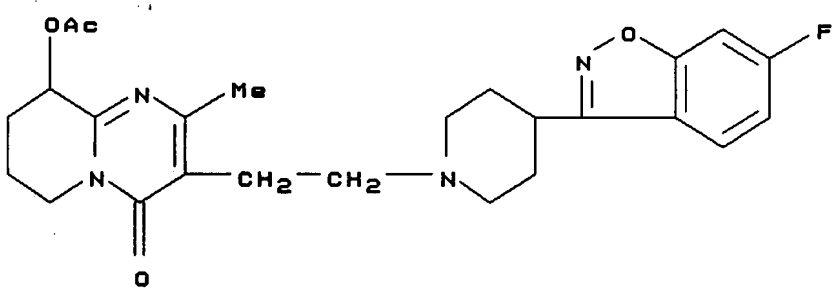
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

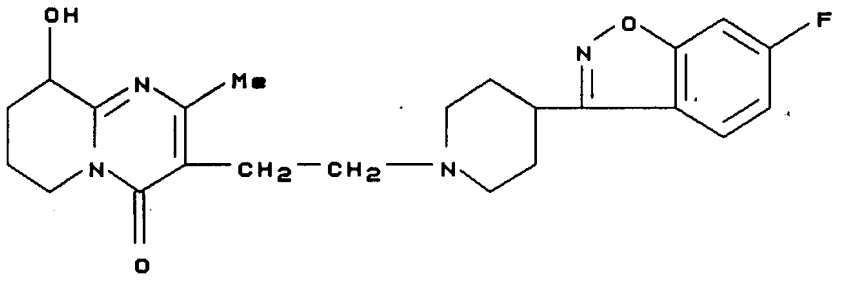
L3 ANSWER 11 OF 18 COPYRIGHT 1992 ACS
RN 130049-87-5 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 9-(acetyloxy)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C25 H29 F N4 O4
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

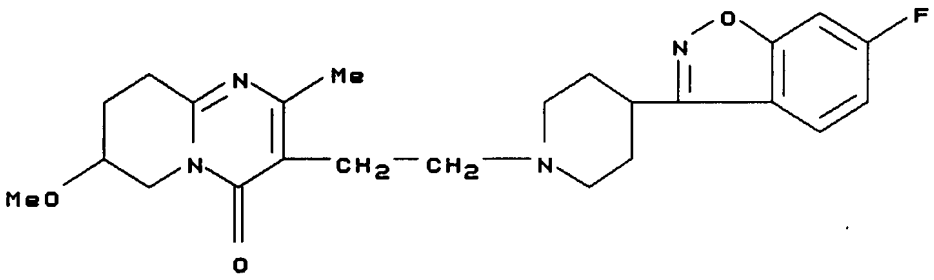
L3 ANSWER 12 OF 18 COPYRIGHT 1992 ACS
RN 130049-86-4 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-, (-)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C23 H28 N4 O3
SR CA
LC CA
DES 3:(-)



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

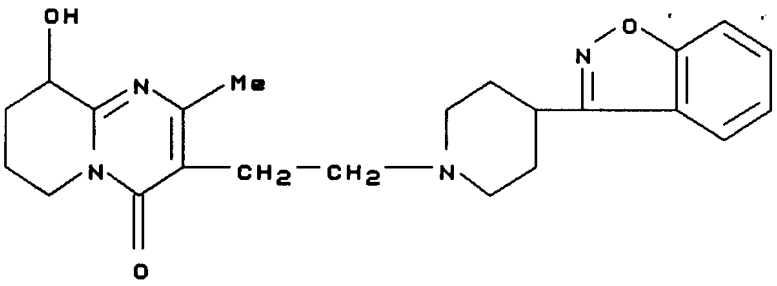
L3 ANSWER 15 OF 18 COPYRIGHT 1992 ACS
RN 130049-83-1 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-7-methoxy-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C24 H29 F N4 O3
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

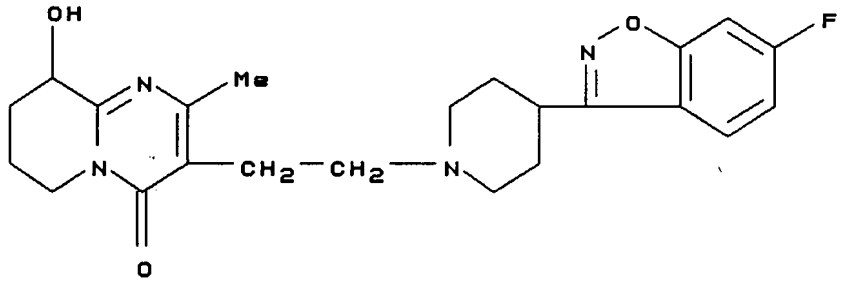
L3 ANSWER 16 OF 18 COPYRIGHT 1992 ACS
RN 106266-11-9 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 6,7,8,9-tetrahydro-3-[2-[4-(6-hydroxy-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C23 H28 N4 O3
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

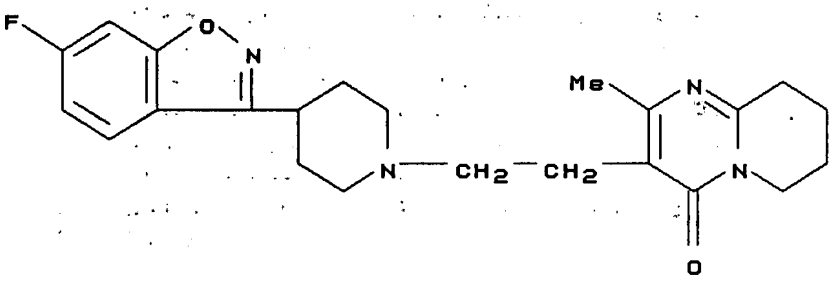
L3 ANSWER 13 OF 18 COPYRIGHT 1992 ACS
RN 130049-85-3 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-, (+)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C23 H27 F N4 O3
SR CA
LC CA
DES 3:(+)



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA113(21):191384n

L3 ANSWER 14 OF 18 COPYRIGHT 1992 ACS
RN 130049-84-2 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-, (.+-.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
MF C23 H27 F N4 O3
SR CA
LC CA
DES 3:(+-)



27 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: CA117(7):62858d

REFERENCE 2: CA116(23):228041p

REFERENCE 3: CA116(23):228039u

REFERENCE 4: CA116(19):187938r

REFERENCE 5: CA116(19):187858q

REFERENCE 6: CA116(17):168781t

REFERENCE 7: P CA116(15):143854f

REFERENCE 8: CA116(13):120780q

REFERENCE 9: CA115(19):198251s

REFERENCE 10: CA115(19):197736s

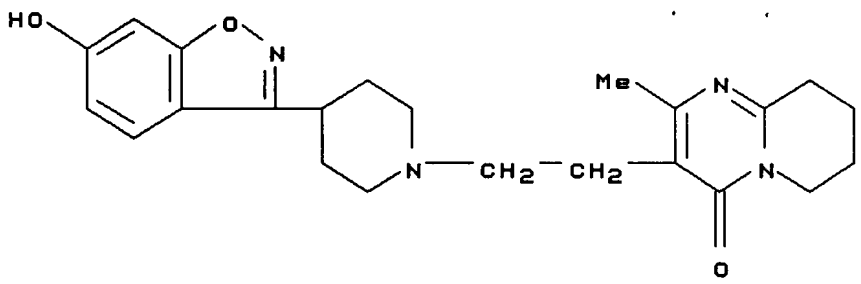
=> fil ca; s l3 or l3/d
FILE 'CA' ENTERED AT 15:44:21 ON 23 SEP 92
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1992 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1967 -20 Sep 92 (920920/ED) VOL 117 ISS 12.
For OFFLINE Prints or Displays, use the ABS or ALL formats to obtain abstract graphic structures. The AB format DOES NOT display structure diagrams.

29 L3
0 L3/D
L4 29 L3 OR L3/D

=> d bib abs hit l4 1-29

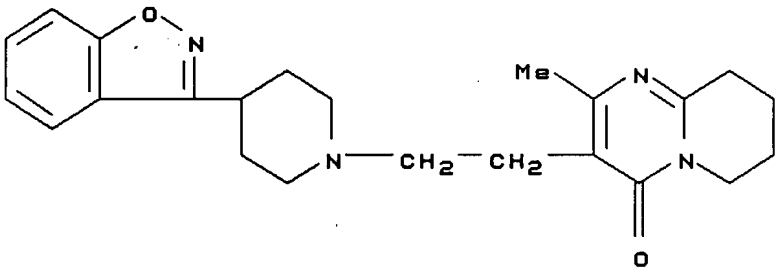
L4 ANSWER 1 OF 29 COPYRIGHT 1992 ACS
AN CA117(7):62858d
TI Antipsychotic profile and side-effect liability of haloperidol, risperidone, and ocaperidone as predicted from their differential interaction with amphetamine in rats
AU Megens, Anton A. H. P.; Niemegeers, Carlos J. E.; Awouters, Frans H. L.
CS Dep. Pharmacol., Janssen Res. Found.
LO Beerse 2340, Belg.
SO Drug Dev. Res., 26(2), 129-45
SC 1-11 (Pharmacology)



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA106(9):67292x

L3 ANSWER 17 OF 18 COPYRIGHT 1992 ACS
RN 106266-09-5 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
FS 3D CONCORD
MF C23 H28 N4 O2
SR CA
LC CA



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P CA106(9):67292x

L3 ANSWER 18 OF 18 COPYRIGHT 1992 ACS
RN 106266-06-2 REGISTRY
CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Benzisoxazole, 4H-pyrido[1,2-a]pyrimidin-4-one deriv. (9CI)
OTHER NAMES:
CN R 64766
CN Risperidone
FS 3D CONCORD
MF C23 H27 F N4 O2
SR CA
LC BIOSIS, CA, CJACS, MEDLINE, PHAR, WHO

Clozapine, fluperlapine, risperidone, setoperone, and ORG5222 had higher occupancy in 5-HT2 than in D2.

IT 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 2709-56-0, Flupenthixol 5786-21-0, Clozapine 15676-16-1, Sulpiride 26615-21-4, Zotepine 67121-76-0, Fluperlapine 75558-90-6, Amperozide 85650-56-2, ORG 5222 86487-64-1, Setoperone 106266-06-2, Risperidone
(dopamine and serotonin receptors of brain binding by)

L4 ANSWER 3 OF 29 COPYRIGHT 1992 ACS
AN CA116(23):228039u
TI Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells
AU Bolden, Carolyn; Cusack, Bernadette; Richelson, Elliott
CS Dep. Psychiatry Psychol., Mayo Clin.
LO Jacksonville, FL, USA
SO J. Pharmacol. Exp. Ther., 260(2), 576-80
SC 1-11 (Pharmacology)
DT J
CO JPETAB
IS 0022-3565
PY 1992
LA Eng
AN CA116(23):228039u
AB The authors detd. the affinity and selectivity of binding for 24 compds.: nine antimuscarinics (including some antiparkinson drugs) and 15 neuroleptics (including the atypical compds. clozapine, fluperlapine, melperone, rilapine, risperidone, tenilapine, tiospirone and zotepine) at the five human muscarinic receptor subtypes expressed in Chinese hamster ovary cells. Equil. dissocn. consts. (Kd) were obtained from competitive radioligand binding studies with [3H]quinuclidinyl benzilate and membrane prepns. of these cells. As expected, QNB had the highest affinity of the compds. studied at the five receptor subtypes and was not selective (Kd ranged from 0.027-0.088 nM). Benztropine had the next highest affinity of the antimuscarinic compds. and thioridazine had the highest affinity of the neuroleptics. Among the antiparkinson drugs, biperiden was the only one selective for the M1 subtype; and among the neuroleptics, the atypical drug clozapine was also selective for the M1 subtype. This selectivity may explain clozapine's unusual efficacy in refractory schizophrenic patients and its low incidence of extrapyramidal side effects. However, because most other atypical neuroleptics studied lacked high affinity and selectivity at muscarinic receptor subtypes, it is likely that other mechanisms are involved as well.

IT 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 51-34-3, Scopolamine 51-55-8, Atropine, biological studies 58-73-1, Diphenhydramine 77-37-2 113-59-7, Chlorprothixene 132-17-2, Benztropine 144-11-6, Trihexyphenidyl 514-65-8 1977-10-2, Loxapine 3313-26-6, cis-Thiothixene 3575-80-2, Melperone 5588-33-0, Mesoridazine 5786-21-0, Clozapine 6581-06-2, QNB 10457-90-6, Bromperidol 26615-21-4 28797-61-7, Pirenzepine 67121-76-0, Fluperlapine 79781-95-6, Rilapine 82650-83-7, Tenilapine 87691-91-6 106266-06-2
(binding of, to human muscarinic receptor subtypes, anticholinergic side-effects in relation to)

L4 ANSWER 4 OF 29 COPYRIGHT 1992 ACS
AN CA116(19):187938r
TI Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT1C receptors

DT J
CO DDREDK
IS 0272-4391
PY 1992
LA Eng
AN CA117(7):62858d
AB Motor activity effects of haloperidol, risperidone, and ocaperidone were studied in rats challenged with amphetamine. At a low dose of amphetamine, the compds. were about equipotent in reducing amphetamine-induced hyperactivity in normal values (lowest ED50s: 0.015-0.023 mg/kg). Haloperidol completely blocked motility at a slightly higher dose (0.14 mg/kg). In contrast, much higher doses of risperidone and ocaperidone were required for complete blockade of motility (ED50s: 2.0 and 1.7 mg/kg, resp.). With increasing dose of amphetamine, risperidone became considerably less potent than haloperidol in reducing hyperactivity; ocaperidone remained at least as potent as haloperidol in this respect. Moreover, risperidone lost, while ocaperidone maintained, its high margin towards complete blockade of motility. The compds. were also equipotent (lowest ED50s: 0.0075-0.0089 mg/kg) in reversing amphetamine-induced behavioral withdrawal (stationary stereotypy) to more environment directed behavior (active exploration). However, this "disinhibitory" effect was maintained over a much wider dose range with risperidone than with haloperidol and ocaperidone. The obsd. differences in interaction with amphetamine are presumably related to relative serotonin 5HT2/dopamine D2 antagonistic activity and suggest important differences in therapeutic profile and side-effect liability of the compds. The implications for distinct clin. applications of the compds. are discussed: risperidone might be the drug of choice for maintenance therapy of chronic schizophrenics, esp. for patients with mild pos. symptoms and type II patients with predominant neg. symptoms and ocaperidone for therapeutic treatment of the pronounced pos. symptoms in acute schizophrenia or during exacerbations of chronic schizophrenia.
IT 52-86-8, Haloperidol 106266-06-2, Risperidone
129029-23-8, Ocaperidone
(amphetamine behavorial effects interaction by, antipsychotic profile and side-effect liability in relation to)

L4 ANSWER 2 OF 29 COPYRIGHT 1992 ACS
AN CA116(23):228041p
TI Dopamine and serotonin receptor occupancy by atypical antipsychotic drugs in vivo
AU Matsubara, Ryoji; Matsubara, Shigehiro; Koyama, Tsukasa; Yamashita, Itaru
CS Sch. Med., Hokkaido Univ.
LO Sapporo 060, Japan
SO Shinkei Seishin Yakuri, 14(2), 145-53
SC 1-11 (Pharmacology)
DT J
CO SSYAD7
IS 0388-7588
PY 1992
LA Japan
AN CA116(23):228041p
AB Binding occupancy of atypical antipsychotic drugs in the dopamine receptors (D1 and D2) and the serotonin receptor (5-HT2) in vivo was detd. with the membrane fractions of the rat striatum and frontal cerebral cortex using radiolabeled SCH23390, spiperone, ketanserin, and an irreversible common ligand, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Generally the atypical antipsychotic drugs were lower in the occupancy in D1 and D2 than the typical drugs.

obsd. with lower doses of amphetamine; 2) inhibition: the first significant redn. of activity; 3) normalization: redn. of activity to the level of nonamphetaminized rats; and 4) suppression: redn. of activity to 50% of the level of nonamphetaminized rats. Ocaperidone and risperidone were equipotent with haloperidol for disinhibition (0.0062-0.011 mg/kg). However, the disinhibition was maintained over a wider dose range with risperidone (factor 84) than with haloperidol (9.0) and ocaperidone (4.1) and was also more pronounced in magnitude with risperidone. Ocaperidone was equipotent with haloperidol for inhibition (0.013-0.025 mg/kg) and normalization (0.074-0.080 mg/kg) for 4.4 times less potent for suppression of activity (0.71 vs. 0.16 mg/kg). Risperidone became progressively less potent than haloperidol: 4.4 times for inhibition, 9.6 times for normalization and 22 times for suppression of activity. The present data are consistent with the hypothesis that serotonin-2 antagonism compensates for the functional consequences of D2 receptor blockade. The implications for the clin. application of the compds. are discussed.

IT 106266-06-2, Risperidone 129029-23-8, Ocaperidone
(amphetamine antagonism by, haloperidol comparison with, serotoninergic S2 antagonism compensation for D2-receptopr block in relation to schizophrenia treatment)

L4 ANSWER 6 OF 29 COPYRIGHT 1992 ACS
AN CA116(17):168781t
TI A predictive model for substrates of cytochrome P450-debrisoquine (2D6)
AU Koymans, Luc; Vermeulen, Nico P. E.; Van Acker, Saskia A. B. E.; Te Koppele, Johan M.; Heykants, Jos J. P.; Lavrijsen, Karel; Meuldermans, Willem; Donne-Op den Kelder, Gabrielle M.
CS Fac. Chem., Free Univ.
LO Amsterdam 1081 HV, Neth.
SO Chem. Res. Toxicol., 5(2), 211-19
SC 7-3 (Enzymes)
SX 1, 6
DT J
CO CRTOEC
IS 0893-228X
PY 1992
LA Eng
OS CJACS
AN CA116(17):168781t
AB Mol. modeling techniques were used to derive a predictive model for substrates of human cytochrome P 450 2D6, an isoform known to metabolize only compds. with .gtoreq.1 basic N atoms. Sixteen substrates, accounting for 23 metabolic reactions, with a distance of either 5 .ANG. (5-.ANG. substrates, e.g., debrisoquine) or 7 .ANG. (7-.ANG. substrates, e.g., dextromethorphan) between oxidn. site and basic N atom were fitted into 1 model by postulating an interaction of the basic N atom with a neg. charged carboxylate group on the protein. This acidic residue anchors and neutralizes the pos. charged basic N atom of the substrates. In case of 5-.ANG. substrates this interaction probably occurs with the carboxylic O atom nearest to the oxidn. site, whereas in the case of 7-.ANG. substrates this interaction takes place at the other O atom. Furthermore, all substrates exhibit a coplanar conformation near the oxidn. site and have neg. mol. electrostatic potentials (MEPs) in a part of this planar domain approx. 3 .ANG. away from the oxidn. site. No common features were found in the neighborhood of the basic N atom of the substrates studied so that this region of the active site can accommodate a variety of N-substituents. Therefore, the substrate specificity of P 450 2D6 most likely is detd. by the

AU Roth, Bryan L.; Ciaranello, Roland D.; Meltzer, Herbert Y.
CS Sch. Med., Stanford Univ.
LO Stanford, CA, USA
SO J. Pharmacol. Exp. Ther., 260(3), 1361-5
SC 1-11 (Pharmacology)
DT J
CO JPETAB
IS 0022-3565
PY 1992
LA Eng
AN CA116(19):187938r
AB The authors detd. the affinities of clozapine and 21 other typical and atypical antipsychotic agents for the cloned 5-hydroxytryptamine-1C (5-HT1C) receptor. For these studies, 5-HT1C receptors were transiently expressed in COS-7 cells using the vector pSVK3-5HT1C. Clozapine and several other putative typical and atypical antipsychotic agents (loxapine > tiospirone > SCH23390 > fluperlapine > rilapine > chlorpromazine) had relatively high affinities (7-30 nM) for the cloned 5-HT1C receptor. Other antipsychotic agents (risperidone > tenilapine > mesoridazine > thioridazine > cis-fluphenthixol) had intermediate affinities (30-100 nM), whereas many other antipsychotics (fluphenazine > spiperone > amperozide > melperone > thiothixene > haloperidol, metoclopramide, pimozide, domperidone, sulpuride) had low affinities (>500 nM) for the cloned 5-HT1C receptor. The results indicate that although several putative atypical antipsychotic agents have high affinities for the cloned rat 5-HT1C receptor, the spectrum of drug binding does not correlate with the atypical nature of these compds.
IT 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 69-23-8, Fluphenazine 364-62-5, Metoclopramide 749-02-0, Spiperone 1977-10-2, Loxapine 2062-78-4, Pimozide 3575-80-2, Melperone 4774-24-7, Quipazine 5588-33-0, Mesoridazine 5591-45-7, Thiothixene 5786-21-0, Clozapine 15676-16-1 53772-82-0 57808-66-9, Domperidone 64022-27-1, MK 212 64795-35-3, Mesulergine 67121-76-0, Fluperlapine 74050-98-9, Ketanserin 75558-90-6, Amperozide 79781-95-6, Rilapine 82650-83-7, Tenilapine 87051-43-2, Ritanserin 87134-87-0, Sch 23390 maleate 87691-91-6 106266-06-2, Risperidone
(cloned serotoninergic S1C receptor binding by, as antipsychotic)

L4 ANSWER 5 OF 29 COPYRIGHT 1992 ACS
AN CA116(19):187858q
TI Behavioral disinhibition and depression in amphetaminized rats: a comparison of risperidone, ocaperidone and haloperidol
AU Megens, A. A. H. P.; Niemegeers, C. J. E.; Awouters, F. H. L.
CS Janssen Res. Found.
LO Beerse 2340, Belg.
SO J. Pharmacol. Exp. Ther., 260(1), 160-7
SC 1-11 (Pharmacology)
DT J
CO JPETAB
IS 0022-3565
PY 1992
LA Eng
AN CA116(19):187858q
AB The mixed serotonin-2/dopamine-D2 antagonists risperidone and ocaperidone were compared with the specific D2 antagonist haloperidol for their ability to antagonize amphetamine (10 mg/kg, s.c.)-induced stereotypy in rats. Four successive stages of amphetamine antagonism were differentiated: 1) disinhibtion: reversal of stationary stereotypy into the hyperactivity normally

L4 ANSWER 8 OF 29 COPYRIGHT 1992 ACS
AN CA116(13):120780q
TI Competitive interactions at [3H]1,3-di(2-tolyl)guanidine (DTG)-defined .sigma. recognition sites in guinea pig brain
AU DeHaven-Hudkins, Diane L.; Fleissner, Lorraine C.
CS Dep. Enzymol. Receptor Biochem., Sterling Winthrop Pharm. Res. Div. LO Malvern, PA 19355-1314, USA
SO Life Sci., 50(9), PL65-PL70
SC 1-11 (Pharmacology)
SX 2
DT J
CO LIFSAK
IS 0024-3205
PY 1992
LA Eng
AN CA116(13):120780q
AB In satn. binding expts., (+)pentazocine, (+)3-(3-hydroxyphenyl)-N-propylpiperidine (3-PPP), haloperidol, and rimcazole did not inhibit the binding of [3H]DTG in a purely competitive fashion. Although Scatchard anal. indicated that [3H]DTG bound to a single site, the inhibition curves of some, but not all, ref. compds. exhibited Hill coeffs. of less than 0.8. The Scatchard data were consistent with a model of hyperbolic competitive inhibition of binding to the [3H]DTG-defined .sigma. site, although other possibilities such as neg. cooperativity or binding to two sites cannot be definitely excluded. Compds. from numerous pharmacol. and structural causes inhibited the binding of [3H]DTG, suggesting that interactions of [3H]DTG with other receptors may have confounded the Scatchard anal. of the binding of [3H]DTG to .sigma. recognition sites.
IT 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 51-64-9 52-53-9, Verapamil 52-86-8, Haloperidol 56-40-6, Glycine, biological studies 56-86-0, L-Glutamic acid, biological studies 57-27-2, Morphine, biological studies 57-42-1 58-25-3, Chlordiazepoxide 58-39-9, Perphenazine 76-74-4, Pentobarbital 77-10-1, Phencyclidine 77-17-8, Normeperidine 91-81-6, Tripelennamine 121-25-5, Amprolium 125-71-3, Dextromethorphan 127-35-5, Phenazocine 132-17-2, Benztropine 146-48-5 146-54-3, Trifluprom azine 298-57-7, Cinnarizine 465-65-6, Naloxone 487-79-6, Kainic acid 630-60-4, Ouabain 1814-64-8, PAPP 2379-57-9, DNQX 7313-86-2, (-).alpha.-Cyclazocine 7313-87-3, (+).alpha.-Cyclazocine 7361-76-4 7488-49-5 14198-28-8, (-)SKF-10,047 21820-30-4, (-)-.beta.-Cyclazocine 21820-35-9, (+)-.beta.-Cyclazocine 23672-07-3, (-)Sulpiride 28797-61-7, Pirenzepine 33507-63-0, Substance P 35386-24-4, 1-(2-Methoxyphenyl)piperazine 50679-08-8, Terfenadine 51152-91-1, (-)Butaclamol 52468-60-7, Flunarizine 52809-07-1 56245-67-1, (+)Butaclamol 58640-82-7, (+)SKF-10,047 58918-32-4, (-)Ethylketocyclazocine 62869-68-5 62869-69-6 67469-78-7, GBR-12909 75859-04-0, Rimcazole 77086-22-7, (+)MK-801 77126-85-3, DIG 77521-29-0, AMPA 78966-69-5 80300-08-9 82117-52-0, HR-375 82785-45-3, Neuropeptide Y 83913-06-8 84774-02-7, (+)Ethylketocyclazocine 85966-89-8, (-)-3-PPP 85976-54-1, (+)3-PPP 87051-43-2, Ritanserin 99755-60-9 105565-56-8, BMY-14802 106266-06-2 108549-42-4, CPP 109028-10-6, CGS 12066B 115066-14-3, CNQX 121917-57-5, (-)MK-801
(at ditolylguanidine-defined .sigma. recognition sites competitive interaction of, in brain)

L4 ANSWER 9 OF 29 COPYRIGHT 1992 ACS
AN CA116(5):41471m

distance between oxidn. site and basic N atom, by steric constraints near the oxidn. site, and by the degree of complementarity between the MEPs of substrate and protein in the planar region adjacent to the oxidn. site. The predictive value of the model was evaluated by investigating the P 450 2D6 mediated metab. of 4 new compds. comprising at least 14 oxidative metabolic routes. According to the model, 4 of the metabolic routes were predicted to be mediated by P 450 2D6, whereas 10 were not. The involvement of P 450 2D6 in these 14 metabolic reactions was investigated in man in vivo and/or in vitro. From these exptl. results it appeared that 3 of the 4 predicted metabolic routes were mediated by P 450 2D6 and 11 were not, closely matching the predictions from the model. Thus, the computer-assisted predictions seem to correlate well with the exptl. results, and hence the presented model may be useful in identifying metabolic pathways that might be subject to the debrisoquine/sparteine type of polymorphism in a very early stage of the development of drugs.

IT 68844-77-9, Astemizole 71195-58-9, Alfentanil 99200-09-6, Nebivolol 106266-06-2, Risperidone
(metab. of, by cytochrome P 450 2D6 monooxygenase of human, structure effect on, predictive model for enzyme substrate specificity in relation to)

L4 ANSWER 7 OF 29 COPYRIGHT 1992 ACS
AN CA116(15):143854f
TI Treatment of cutaneous hypersensitivity with topical calcium channel blockers
AU Sharpe, Richard J.; Arndt, Kenneth A.; Galli, Stephen J.
CS Beth Israel Hospital Assoc.
LO USA
SO S. African, 23 pp.
PI ZA 9006583 A 25 Sep 1991
AI ZA 90-6583 20 Jul 1990
PRAI US 89-396846 21 Aug 1989
IC ICM A61K
ICS C07D
SC 1-7 (Pharmacology)
SX 63
DT P
CO SFXXAB
PY 1991
LA Eng
AN CA116(15):143854f
AB Ca channel blockers are used topically for inhibition of cutaneous, ocular, or mucosal hypersensitivity reactions, inflammation, hyperproliferation, or scarring. Mice were sensitized to 3% oxazolone (I) by applying I to the abdomen and hind footpad. On the day of treatment, each side of both ears were challenged with I. Nifedipine (II) was applied to each side of a given ear 1 h after challenge. II reduced the I-induced inflammation significantly after 24 h as compared to control.

IT 50-55-5, Reserpine 129-03-3, Cyproheptadine 288-32-4D, Imidazole, derivs. 361-37-5 749-02-0, Spiperone 1166-34-3, Cinanserine 1400-61-9, Nystatin 1893-33-0, Pipamperone 19794-93-5, Trazodone 23593-75-1, Clotrimazole 24219-97-4, Mianserin 27220-47-9 41621-49-2, Ciclopirox olamine 60634-51-7, LY 53857 61318-90-9 64211-45-6, Oxiconazole 65277-42-1 65472-88-0, Naftifine 74050-98-9, Ketanserin 84625-61-6, Itraconazole 85273-96-7 87051-43-2, Ritanserin 106266-06-2, Risperidone 108674-87-9, LY 281067
(cutaneous hypersensitivity inhibition with topical calcium channel blockers and)

(prepn. of, as antipsychotic)

L4 ANSWER 10 OF 29 COPYRIGHT 1992 ACS
AN CA115(19):198251s
TI Comparison of the effects of various typical and atypical antipsychotic drugs on the suppressant action of 2-methylserotonin on medial prefrontal cortical cells in the rat
AU Ashby, Charles R., Jr.; Minabe, Yoshio; Edwards, Emmeline; Wang, Rex Y.
CS Dep. Psychiatry Behav. Sci., State Univ. New York
LO Stony Brook, NY 11794-8790, USA
SO Synapse (N. Y.), 8(3), 155-61
SC 1-11 (Pharmacology)
DT J
CO SYNAET
IS 0887-4476
PY 1991
LA Eng
AN CA115(19):198251s
AB The effects of various typical and atypical antipsychotic drugs (APDs) on the suppressant action of microiontophoretically applied 2-methylserotonin (2-Me-5HT, a 5-HT3 agonist) on medial prefrontal cortical (mPFc) cells was studied. The microiontophoresis of 2-Me-5HT (10-80 nA) produced a current-dependent suppression of mPFc cells' firing, and this effect was blocked by various 5-HT3 antagonists. The microiontophoresis of the atypical APDs clozapine and a structurally related compd., RMI 81,582, mimicked the action of the 5-HT3 antagonists. In addn., the i.v. administration of clozapine and RMI 81,582 antagonized the suppressant action produced by the iontophoretic application of 2-Me-5HT on mPFc cells. However, the suppressant action of 2-Me-5HT was not blocked by the typical APDs haloperidol and chlorpromazine. The putative atypical APDs risperidone, setoperone, CL 77328, SCH 23390, CGS 10746B, 1-sulpiride, and thioridazine were ineffective in antagonizing 2-Me-5HT's action. Overall, these results suggest that the majority of putative atypical APDs do not interact with 5-HT3 binding sites in the brain. Whether the interaction of clozapine and RMI 81,582 with 5-HT3 sites is correlated with their therapeutic efficacy or lower potential to induce neurol. side effects remains to be detd.
IT 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 5786-21-0, Clozapine 15676-16-1 39051-50-8 67449-00-7, CL 77328 81382-52-7, CGS 10746B 86487-64-1, Setoperone 87075-17-0, SCH 23390 106266-06-2, Risperidone
(serotoninergic neurotransmission in brain medial prefrontal cortex response to, S3 receptor mediation of)

L4 ANSWER 11 OF 29 COPYRIGHT 1992 ACS
AN CA115(19):197736s
TI Behavioral effects of D1 and D2 dopamine receptor antagonists in squirrel monkeys
AU Bergman, Jack; Madras, Bertha K.; Spealman, Roger D.
CS New England Reg. Primate Res. Cent., Harvard Med. Sch.
LO Southborough, MA 01772-9012, USA
SO J. Pharmacol. Exp. Ther., 258(3), 910-17
SC 1-3 (Pharmacology)
DT J
CO JPETAB
IS 0022-3565
PY 1991
LA Eng
AN CA115(19):197736s

TI Preparation of 3-[(benzisoxazolylpiperidino)alkyl]-4H-pyrido[1,2-a]pyrimidin-4-ones as antipsychotics

AU Kennis, Ludo Edmond Josephine; Vandenberk, Jan; Van Heertum, Albertus Hendricus Maria Theresia

CS Janssen Pharmaceutica N. V.

LO Belg.

SO Eur. Pat. Appl., 22 pp.

PI EP 453042 A1 23 Oct 1991

DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE

AI EP 91-200897 16 Apr 1991

PRAI GB 90-8850 19 Apr 1990

IC ICM C07D471-04
ICS A61K031-505

ICI C07D471-04, C07D239-00, C07D221-00

SC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

SX 1

DT P

CO EPXXDW

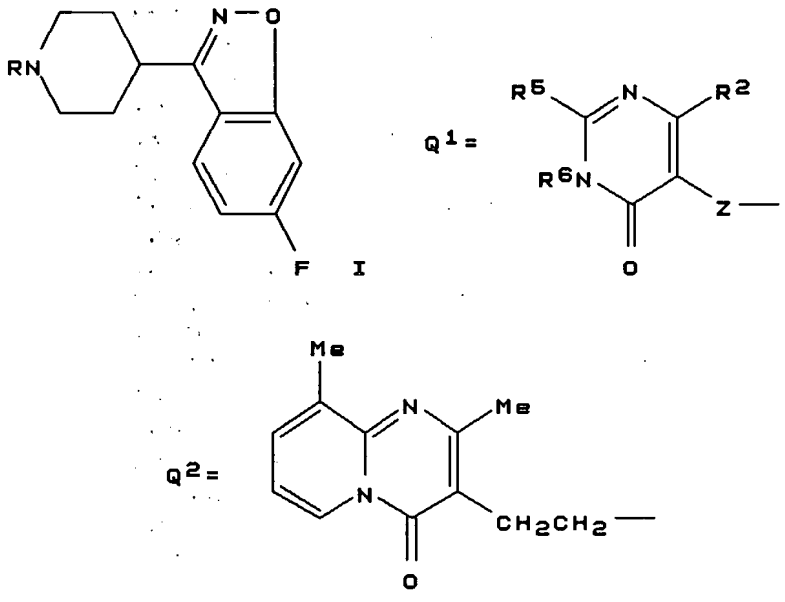
PY 1991

LA Eng

OS MARPAT 116:41471

AN CA116(5):41471m

GI



AB Title compds. [I; R = Q1 wherein R2 = H, alkyl; R5R6 = R1C:CHCH:CH, R3CH(CH2)3, C(:CHR4)(CH2)3; R1 = (hydroxy)alkyl, CHO, CO2H, alkanoyloxyalkyl; R3 = (hydroxy)alkyl, PhCH2, 3-pyridiylmethyl, 5-methyl-2-furanylmethyl; R4 = alkyl, pH, 3 pyridyl, 5-methyl-2-furanyl; Z = alkylene] were prepd. Thus, I (R = H) was condensed with Q2Br to give I (R = Q2) which had oral ED50 of 0.0063 mg/kg for antiemetic effect when administered 32 h before apomorphine challenge in dogs.

IT 129029-23-8P 138271-01-9P 138271-02-0P
138271-03-1P 138271-04-2P 138271-05-3P
138271-06-4P 138271-07-5P 138271-08-6P
138271-09-7P 138271-10-0P 138271-11-1P

antiischemic agents by affecting the N-methyl-D-aspartate receptor complex.

IT 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 58-38-8, Prochlorperazine 58-39-9, Perphenazine 60-99-1, Levomepromazine 69-23-8, Fluphenazine 77-23-6, Carbetapentane 125-71-3 153-87-7, Oxypertine 298-57-7, Cinnarizine 728-88-1, Tolperisone 749-02-0, Spiperone 1050-79-9, Moperone 1893-33-0, Pipamperone 2062-78-4 2622-26-6, Propericiazine 3703-76-2, Cloperastine 5942-95-0 10457-90-6, Bromperidol 23210-56-2, Ifenprodil 26615-21-4 26864-56-2, Penfluridol 34104-67-1 47739-98-0 52468-60-7, Flunarizine 53583-79-2, Sultopride 57648-21-2, Timiperone 64840-90-0, Eperisone 75272-39-8, YM-09151-2 75859-04-0 80125-14-0, Remoxipride 98043-60-8, Y-516 105565-56-8, BMY-14802 106266-06-2
(brain .sigma.-receptor binding of, pharmacol. specificity in relation to)

L4 ANSWER 13 OF 29 COPYRIGHT 1992 ACS
AN CA115(10):99299g
TI Method and composition for the treatment of cutaneous, ocular, and mucosal hypersensitivity, inflammation, and hyperproliferative conditions using topical preparations of serotonin antagonists
AU Sharpe, Richard J.; Arndt, Kenneth A.; Galli, Stephen J.
CS Beth Israel Hospital Assoc.
LO USA
SO PCT Int. Appl., 31 pp.
PI WO 9102527 A1 7 Mar 1991
DS W: AU, CA, FI, JP, NO
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE
AI WO 90-US4637 15 Aug 1990
PRAI US 89-396523 21 Aug 1989
US 90-494744 16 Mar 1990
IC ICM A61K031-44
SC 63-6 (Pharmaceuticals)
SX 1
DT P
CO PIXXD2
PY 1991
LA Eng
OS MARPAT 115:99299
AN CA115(10):99299g
AB Topical compns. contg. serotonin antagonists are effective for the treatment of cutaneous or mucosal disease involving hypersensitivity, inflammation, scarring, or epithelial hyperproliferation. The serotonin antagonist is selected from the group consisting of reserpine, ketanserin, cyproheptadine, spiperone, methysergide, LV 53857, ritanserin, ICI 169369, risperidone, pipamperone, trazodone, cinanserine, mianserin, and LY 281067. A 3.7% reserpine soln. in a mixt. contg. Na laureth sulfate 1, isopropanol 4, EtOH 47.5, propylene glycol 37.5, and water to 100% was prepd. and 20 .mu.L of the soln. was applied to the ears of mice having oxazolone-induced contact hypersensitivity; the prepn. significantly reduced the oxazolone-induced inflammation.

IT 50-55-5 129-03-3, Cyproheptadine 361-37-5, Methysergide 749-02-0, Spiperone 1166-34-3, Cinanserine 1893-33-0, Pipamperone 19794-93-5, Trazodone 24219-97-4, Mianserin 60634-51-7 74050-98-9, Ketanserin 85273-96-7 87051-43-2, Ritanserin 106266-06-2 108674-87-9, LY 281067 135702-21-5
(topical compn. contg., for treatment of cutaneous and mucosal diseases)

AB The behavioral effects of dopamine antagonists differing in affinity and selectivity at D1 and D2 dopamine receptors were compared in squirrel monkeys responding under a fixed-interval schedule to stimulus-shock termination. D1-selective antagonists included SCH 23390, SCH 23388, SCH 39166, R-SKF 83566, R-SKF 83692, and RS-SKF 83692. D2-selective antagonists included YM-09151-2, eticlopride, raclopride, haloperidol, risperidone, remoxipride, S-sulpiride, and R-sulpiride; nonselective dopamine antagonists were S-butaclamol and chlorpromazine. Regardless of selectivity for D1 or D2 receptors, all drugs produced dose-related decreases in fixed-interval responding. A high degree of stereoselectivity was evident for both D1 antagonists (the (R)-enantiomers SCH 23390 and R-SKF 83692 were more potent than the resp. (S)-enantiomers SCH 23388 and RS-SKF 83692) and D2 antagonists (S-sulpiride more potent than R-sulpiride). High doses of the D1 and D2 antagonists also reduced motor activity and impaired coordination in monkeys in the home cage after test sessions. In combination with the results of radioligand binding expts. conducted in the present study and by B. Madras et al (1988), the findings revealed significant pos. correlations between the potencies of D1 and D2 antagonists for decreasing schedule-contolled behavior and for binding to D1 and D2 receptors, resp. The results suggest that the effects of D1 and D2 antagonists on schedule-controlled behavior are mediated predominantly by the subtype of receptor to which they selectively bind.

IT 23672-07-3, S-Sulpiride 23756-79-8, R-Sulpiride 74050-97-8, Haloperidol decanoate 75272-39-8 80125-14-0, Remoxipride 84226-12-0, Eticlopride 98185-20-7, Raclopride tartrate 106266-06-2
(behavioral effects of, dopamine D2 receptor antagonist activity in relation to)

L4 ANSWER 12 OF 29 COPYRIGHT 1992 ACS
AN CA115(15):150182t
TI Pharmacological specificity of antipsychotic, antiischemic and some other drug for .sigma. receptors labeled with [3H]haloperidol
AU Zushi, Yoshifumi
CS Med. Sch., Okayama Univ.
LO Okayama 700, Japan
SO Okayama Igakkai Zasshi, 103(4), 281-92
SC 1-11 (Pharmacology)
DT J
CO OIZAAV
IS 0030-1558
PY 1991
LA Japan
AN CA115(15):150182t
AB Specific binding of [3H]haloperidol (HPD) in the presence of 25 nM spiperone was saturable and of high affinity (Kd = 1.96 .+-. 1.31 nM, Bmax = 2.37 .+-. 0.27 pmol/mg protein, n = 8). Among the 29 antipsychotics tested in inhibition studies, bromoperidol and HPD were the most post inhibitors (Ki = 0.9 nM, 1.0 nM, resp.). The conventional antipsychotics moperone, timiperone etc. and the novel promising drugs YM-09151, Y-516, BMY-14802, and remoxipride potently inhibited [3H]HPD binding with the Ki in the range of low to moderate nanomolar. On the other hand, among the other 27 drugs tested, the antispasmodics eperisone and tolperisone, the antiischemic agents ifenprodil, the Ca2+ antagonist fluranizine and cinnarizine, and the antitussive carbetapentanece, cloperastine, and dextromethorphan were esp. potent inhibitors. These results suggest that .sigma. receptors may be potential sites of action for anti-ischemic as well as antipsychotic drugs, i.e., .sigma. receptors mediate the neuroprotective effects of certain

HVA levels. MeODMT had no effect on the striatal DA release and metab.

IT 1019-45-0, 5-Methoxy-N,N-dimethyltryptamine 15676-16-1, Sulpiride 36505-84-7, Buspirone 87051-43-2, Ritanserin 106266-06-2, Risperidone
(brain striatal dopamine metab. response to)

L4 ANSWER 16 OF 29 COPYRIGHT 1992 ACS
AN CA114(5):35943j
TI Binding of typical and atypical antipsychotics to 5-HT1C and 5-HT2 sites: clozapine potently interacts with 5-HT1C sites
AU Canton, Herve; Verriele, Laurence; Colpaert, Francis C.
CS Neurobiol. Div., FONDAX
LO Puteaux 92800, Fr.
SO Eur. J. Pharmacol., 191(1), 93-6
SC 1-11 (Pharmacology)
DT J
CO EJPHAZ
IS 0014-2999
PY 1990
LA Eng
AN CA114(5):35943j
AB The affinity of several typical and atypical antipsychotics for the 5-HT1C and 5-HT2 sites was detd. using radioligand binding assays. Most of the antipsychotics tested appeared to bind to 5-HT2 sites with affinities that were fairly high (i.e. pK1 values between 7 and 9) and significantly higher than for 5-HT1C sites. In contrast, clozapine was found to have a significantly higher affinity for 5-HT1C than for 5-HT2 sites. Clozapine had the highest affinity for 5-HT1C sites of all the compds. tested. These findings are consistent with the hypothesis that an interaction with 5-HT2 receptors may be relevant to the clin. activity of typical antipsychotics. The findings also suggest, however, that an interaction with 5-HT1C sites may be relevant to the mechanism of clin. action of clozapine and, perhaps, of other atypical antipsychotics.

IT 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 60-99-1, Levomepromazine 69-23-8, Fluphenazine 749-02-0, Spiperone 1841-19-6, Fluspirilene 5786-21-0, Clozapine 23672-07-3, (-)-Sulpiride 84225-95-6, Raclopride 87691-91-6, Tiospirone 106266-06-2, Risperidone
(serotoninergic S1C and S2 receptors binding by)

L4 ANSWER 17 OF 29 COPYRIGHT 1992 ACS
AN CA113(21):191384n
TI Preparation of 3-[(4-oxopyrido[1,2-a]pyrimidin-3-yl)piperidin-4-yl]1,2-benzisoxazoles as antipsychotics
AU Janssen, Cornelus Gerardus Maria; Knaeps, Alfonsus Guilielmus; Kennis, Ludo Edmond Josephine; Vandenberk, Jan
CS Janssen Pharmaceutica N. V.
LO Belg.
SO Eur. Pat. Appl., 18 pp.
PI EP 368388 A2 16 May 1990
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 89-202724 30 Oct 1989
PRAI US 88-267857 7 Nov 1988
IC ICM C07D471-04
ICS A61K031-505
ICI C07D471-04, C07D239-00, C07D221-00
SC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63

L4 ANSWER 14 OF 29 COPYRIGHT 1992 ACS
AN CA115(3):22136u
TI Prepulse inhibition as a screening test for potential antipsychotics
AU Rigdon, Greg C.; Viik, Kaido
CS Pharmacol. Div., Burroughs Wellcome Co.
LO Research Triangle Park, NC 27709, USA
SO Drug Dev. Res., 23(1), 91-9
SC 1-11 (Pharmacology)
DT J
CO DDREDK
IS 0272-4391
PY 1991
LA Eng
AN CA115(3):22136u
AB The startle response amplitude is greatly reduced by a low intensity pulse presented 100 ms prior to the startle stimulus. The magnitude of this prepulse inhibition (PPI) is reduced in schizophrenic patients. In rats, apomorphine disrupts PPI and haloperidol antagonizes apomorphine effects. The antipsychotic drugs haloperidol, chlorpromazine, clozapine, and risperidone and the non-antipsychotic psychopharmacol. agents diazepam, buspirone, and imipramine were tested for their ability to antagonize the apomorphine effect on PPI of the acoustic startle reflex. Haloperidol, chlorpromazine, and risperidone antagonized the apomorphine blockade of PPI. Clozapine antagonized apomorphine effect only at a dose that decreased startle amplitude by 82%. Imipramine and diazepam did not antagonize the apomorphine effect at behaviorally relevant doses. Buspirone weakly antagonized the apomorphine blockade of PPI, but disrupted PPI when given alone. This PPI test may provide a useful screening procedure for compds. with antipsychotic activity. The lack of a robust clozapine effect needs to be further investigated.
IT 50-49-7, Imipramine 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 439-14-5, Diazepam 5786-21-0, Clozapine 36505-84-7, Buspirone 106266-06-2, Risperidone
(startle reflex inhibition reversal by apomorphine and response to, antipsychotics screening in relation to)

L4 ANSWER 15 OF 29 COPYRIGHT 1992 ACS
AN CA115(3):22126r
TI Microdialysis study of effects of atypical neuroleptics and anxiolytics on striatal dopamine release and metabolism in awake rats
AU Bogdanov, M. B.; Guinetdinov, R. R.; Kudrin, V. S.; Medvedev, O. S.; Val'dman, A. V.
CS Inst. Pharmacol.
LO Moscow, USSR
SO Byull. Eksp. Biol. Med., 111(5), 505-7
SC 1-11 (Pharmacology)
DT J
CO BEBMAE
IS 0365-9615
PY 1991
LA Russ
AN CA115(3):22126r
AB Using brain microdialysis in awake rats, the effects of risperidone, ritanserin, buspirone, sulpiride and 5-methoxy-N,N-dimethyltryptamine (MeODMT) on brain striatal dopamine (DA) release and metab. were studied. Risperidone, sulpiride, and buspirone increased the levels of DA, DOPAC and homovanillic acid (HVA). Ritanserin failed to affect DA release, while it increased DOPAC and

and the 5-HT2 and catecholamine (CA)-antagonist risperidone were tested for stimulus generalization with, and possible antagonism of, the discriminative stimulus properties of the various training drugs. With both drugs at all doses tested, no stimulus generalization was obsd. with any of the training drugs. Ritanserin completely blocked the discriminative stimulus properties of LSD at 40.00 mg/kg but was, at doses up to 40.00 mg/kg, unable to block the discriminative stimulus properties of any of the other training drugs. Risperidone completely antagonized the stimulus properties of LSD and d-amphetamine, partially blocked cocaine, and possessed minor effects on 8-OHDPAT and fentanyl. Whereas ritanserin was almost without effects or response rate, risperidone reduced response rate at doses starting between 0.16 and 0.63 mg/kg. However, the complete antagonism of LSD and d-amphetamine was obsd. without effects on response rate. Globally, these results confirm ritanserin as a selective 5-HT2 antagonist without effects on conditioned behavior. Risperidone was found to be a potent 5-HT2 and DA antagonist, affecting conditioned behavior by interfering with response rate and with the response-reinforcement contingency.

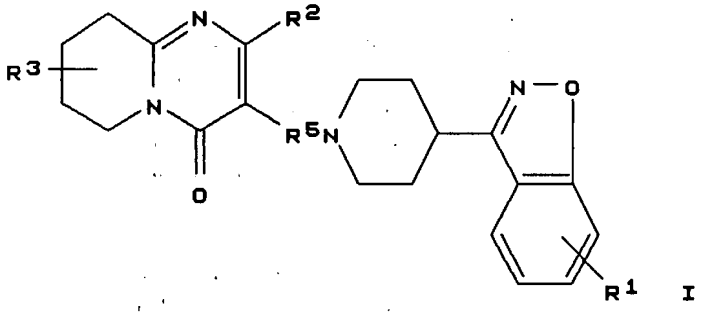
IT 87051-43-2, Ritanserin 106266-06-2, Risperidone
(discriminative behavior response to, drugs interaction with)

L4 ANSWER 19 OF 29 COPYRIGHT 1992 ACS
AN CA112(9):69853d
TI Differential effects of the new antipsychotic risperidone on sleep and wakefulness in the rat
AU Dugovic, C.; Wauquier, A.; Janssen, P. A. J.
CS Dep. Neuropsychopharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO Neuropharmacology, 28(12), 1431-3
SC 1-11 (Pharmacology)
DT J
CO NEPHBW
IS 0028-3908
PY 1989
LA Eng
AN CA112(9):69853d
AB The effects of risperidone, a new antipsychotic with potent-5-hydroxytryptamine2 (5-HT2) and dopamine-D2 (DA-D2) antagonistic properties, were studied on sleep-wakefulness patterns in rats. Administration of low doses (0.01-0.16 mg/kg i.p.) resulted in an increase of deep slow wave sleep (SWS2) and a decrease of wakefulness (W) and light slow wave sleep (SWS1). High doses (0.63-2.5 mg/kg) produced opposite effects. Paradoxical sleep (PS) was reduced over the dose range tested. The increase of SWS2 after low doses of risperidone could be related to a predominant and potent 5-HT2 receptor blocking activity.

IT 106266-06-2, Risperidone
(sleep and wakefulness response to, as antipsychotic)

L4 ANSWER 20 OF 29 COPYRIGHT 1992 ACS
AN CA112(5):30503q
TI Therapeutic effect and safety of increasing doses of risperidone (R 64766) in psychotic patients
AU Mesotten, F.; Suy, E.; Pietquin, M.; Burton, P.; Heylen, S.; Gelders, Y.
CS Psychiatr. Inst. St. Jozef
LO Munsterbilzen B-3751, Belg.
SO Psychopharmacology (Berlin), 99(4), 445-9
SC 1-11 (Pharmacology)
DT J
CO PSCHDL

DT P
CO EPXXDW
PY 1990
LA Eng
OS MARPAT 113:191384
AN CA113(21):191384n
GI



I

AB Title compds. I (R1 = C1-4 alkyl, H, halo; R2 = C1-4 alkyl; R3 = HO, R4CO2, R4 = C1-19 alkyl; R5 = C1-4 alkanediyl) are prepd. 3-(2-Chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one, 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole.HCl, Me2CHNHCHMe2 and MeOH were stirred overnight at 60.degree. to give I (R1 = 6-F; R2 = Me; R3 = 9-HO; R5 = Et) (II). Antipsychotic activity was demonstrated in the combined apomorphine, tryptamine and norepinephrine test in rats or the apomorphine test in dogs. The ED50's for II [apomorphine, tryptamine (convulsion, hyperemia), norepinephrine] were 0.25, 0.31, 0.002, 0.08, mg/kg, resp. Pharmaceutical formulations of I are presented.

IT 130049-82-0P 130049-83-1P 130049-84-2P
130049-85-3P 130049-86-4P 130049-87-5P
130049-88-6P 130049-89-7P 130049-90-0P
(prepn. of, as antipsychotic)

L4 ANSWER 18 OF 29 COPYRIGHT 1992 ACS
AN CA113(3):17815u
TI Pharmacological validation of ritanserin and risperidone in the drug discrimination test procedure in the rat
AU Meert, Theo F.; De Haes, Patrick L. A. J.; Vermote, Patrick C. M.; Janssen, Paul A. J.
CS Dep. Neuropsychopharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO Drug Dev. Res., 19(4), 353-73
SC 1-11 (Pharmacology)
DT J
CO DDREDK
IS 0272-4391
PY 1990
LA Eng
AN CA113(3):17815u
AB The results presented here indicate that 0.16 mg/kg LSD, 2.50 mg/kg 9-OHDPAT, 1.25 mg/kg d-amphetamine, 10.00 mg/kg cocaine, 40.00 mg/kg chlordiazepoxide, 2.50 mg.kg xylazine, nd 0.04 mg/kg fentanyl can be used as disriminative stimuli in a two-lever drug discrimination test procedure in the rat. The central 5-HT2 antagonist ritanserin

IT 87051-43-2, Ritanserin 106266-06-2, Risperidone
(receptor occupancy in pharmacol. of, in brain)

L4 ANSWER 22 OF 29 COPYRIGHT 1992 ACS
AN CA111(21):186795b
TI Benzisoxazole analogues - antipsychotic effects of risperidone (R64766)
AU Harada, Toshiki
CS Med. Sch., Okayama Univ.
LO Okayama 700, Japan
SO Shinkei Seishin Yakuri, 11(9), 677-83
SC 1-0 (Pharmacology)
DT J
CO SSYAD7
IS 0388-7588
PY 1989
LA Japan
AN CA111(21):186795b
AB After brief introduction of the development history of resperidone, its main pharmacol. properties and mechanism of action, pharmacokinetics in man, and clin. effects were briefly reviewed; 15 refs.
IT 106266-06-2, R 64766
(antipsychotic effects of)

L4 ANSWER 23 OF 29 COPYRIGHT 1992 ACS
AN CA111(3):17583a
TI Interaction of haloperidol and risperidone (R 64 766) with amphetamine-induced motility changes in rats
AU Megens, Anton A. H. P.; Awouters, Frans H. L.; Niemegeers, Carlos J. E.
CS Dep. Pharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO Drug Dev. Res., 17(1), 23-33
SC 1-11 (Pharmacology)
DT J
CO DDREDK
IS 0272-4391
PY 1989
LA Eng
AN CA111(3):17583a
AB The interaction of the new antipsychotic risperidone (RIS) and haloperidol (HAL) with amphetamine (I) was studied in rats using an activity meter which measured horizontal, vertical, and stationary components of rats using an activity meter which measured horizontal, vertical, and stationary components of motility. All 3 components increased markedly and progressively after I doses between 0.63-5.00 mg/kg (hyperactivity dose range). At still higher doses of 10.0-80.0 mg/kg, stationary movements (reflecting stereotype) further increased, whereas horizontal activity was much reduced and vertical activity virtually abolished. Both HAL and RIS were potent I antagonists. Doses on the order of 0.02-0.04 mg/kg reduced hyperactivity and reversed stereotypy to a mobility pattern equiv. to that of a lower I dose. Both compds. were able to restore normal motility at any dose level of I stimulation. At the lowest dose of I (0.63 mg/kg), the required normalization doses were comparable for HAL (0.022-0.046 mg/kg) and RIS (0.034-0.16 mg/kg). In order to normalize motility induced by higher I doses up to 5.00 mg/kg, however, a relatively small dose increment of HAL (to 0.045-0.071 mg/kg), but a large dose increment of RIS (to 0.50-0.96 mg/kg) was required. In other words, the dose-normalization curves of RIS and HAL diverged at low doses of I (0.63-5.0 mg/kg). At

IS 0033-3158
PY 1989
LA Eng
AN CA112(5):30503q
AB Risperidone (R 64766) was administered during 4 wk in increasing doses to 17 psychotic patients, to evaluate the hematol. and cardiovascular safety, the therapeutic effect, side effects, effects upon endocrinol. parameters and the pharmacokinetic profile. Following a placebo wash-out period of 1 wk, the initial dose was 10 mg daily, increasing with 5 mg per wk until the maximal dose of 25 mg daily was reached during the 4th week of treatment. Doses up to 20 mg daily resulted in a significant improvement of the total Brief Psychiatric Rating Scale (BPRS) score and of the different BPRS factor scores; with higher doses, no further clin. benefit was achieved except for the hostility and anxiety-depression factor, while sedation became more prominent. No increase of extrapyramidal symptoms was noticed. Except for the sedation obsd. with higher doses, risperidone was well tolerated. No clin. relevant effects on cardiovascular and ECG parameters were noticed, and except for a slight increase of aspartate aminotransferase and alanine aminotransferase in one patient, no lab. abnormalities were obsd. Prolactin showed an expected increase, while the other endocrinol. parameters revealed no changes. Risperidone had a linear pharmacokinetic profile.
IT 106266-06-2, Risperidone
(pharmacokinetics and pharmacol. and toxicity of, in psychosis in humans)

L4 ANSWER 21 OF 29 COPYRIGHT 1992 ACS
AN CA111(25):225196d
TI Receptor occupancy by ritanserin and risperidone measured using ex vivo autoradiography
AU Schotte, Alain; De Bruyckere, Krista; Janssen, Paul F. M.; Leysen, Josee E.
CS Dep. Biochem. Pharmacol., Janssen Res. Found.
LO Beerse, Belg.
SO Brain Res., 500(1-2), 295-301
SC 1-11 (Pharmacology)
DT J
CO BRREAP
IS 0006-8993
PY 1989
LA Eng
AN CA111(25):225196d
AB Autoradiog. techniques are introduced to investigate the occupancy of serotonin 5-HT2, dopamine D2 and .alpha.1-adrenergic receptors after the in vivo administration of ritanserin, a selective, potent and long-acting 5-HT2 antagonist and of risperidone, a very potent 5-HT2 antagonist and potent D2 and .alpha.1 antagonist. Unoccupied 5-HT2 and .alpha.1-receptors were labeled with [125I]7-amino-8-iodoketanserin and D2 receptors with [125I]iodosulpride in horizontal rat brain section. Ritanserin produced 50% occupancy of the 5-HT2 receptors at a dose of 0.02 mg/kg s.c., while at 40 mg/kg s.c. ritanserin still did not occupy 50% of the D2 and .alpha.1 receptors. Risperidone occupied 50% of the 5-HT2, .alpha.1 and D2 receptors at 0.0075, 0.32 and 2.5 mg/kg s.c., resp. Ex vivo autoradiog. was applicable where radioligand binding techniques using brain homogenates had failed for the study of ex vivo receptor occupancy due to rapid drug dissocn. Ex vivo autoradiog. is hitherto the sole technique which allowed the measurement of .alpha.1 receptor occupancy by risperidone after in vivo administration of the drug.

ritanserin and to the dopamine-D2 antagonist haloperidol. The in vitro receptor binding (neurotransmitter-, peptide- and ion channel binding sites) and neurotransmitter uptake profile were investigated. Risperidone revealed, like ritanserin, a very high binding affinity for 5-hydroxytryptamine2 receptors (Ki = 0.16 and 0.30 nM, resp.) and a slow dissocn. (half-time, 31 and 160 min). In accordance, risperidone (IC50 = 0.5 nM) and ritanserin (IC50 = 1.8 nM) potently blocked serotonin-induced 32P-phosphatidic acid formation in human blood platelets. Risperidone showed, like haloperidol, high binding affinity for dopamine-D2 receptors (Ki = 3.13 and 1.55 nM, resp.) and rapid dissocn. (half-time, 2.7 and 5.8 min). Risperidone displayed higher binding affinity than ritanserin and haloperidol for .alpha.-1 adrenergic (Ki = 0.8 nM), histamine-H1 (Ki = 2.23 nM) and .alpha.-2 adrenergic receptors (Ki = 7.54 nM). In in vitro superfusion expts., risperidone and haloperidol reversed at nanomolar concns. the inhibition by LY 171555 (a dopamine-D2 agonist) and by amphetamine of potassium and elec. evoked release of [3H]acetylcholine from striatal slices (postsynaptic dopamine-D2 effects). Both drugs reversed with similar potency the inhibition by LY 171555 of elec. evoked release of [3H]dopamine (a presynaptic dopamine-D2 effect). Risperidone did not affect the activation by amphetamine of [3H]dopamine efflux from rat striatal slices. Risperidone enhanced at nanomolar concns. the stimulated [3H]norepinephrine efflux from cortical slices and its similarly reversed the inhibition by clonidine, at concns. corresponding to its binding affinity for .alpha.-2 adrenergic receptors. The in vitro biochem. properties of risperidone are in agreement with the reported in vivo pharmacol. profile, and the relation to clin. findings is discussed.

IT 106266-06-2, Risperidone
(binding of, to neurotransmitter receptors in brain)

L4 ANSWER 26 OF 29 COPYRIGHT 1992 ACS
AN CA109(25):222341v
TI Partial and complete blockade of 5-hydroxytryptophan (5-HTP)-induced head twitches in the rat: a study of ritanserin (R 55 667), risperidone (R 64 766), and related compounds
AU Meert, Theo F.; Niemegeers, Carlos J. E.; Awouters, Frans; Janssen, Paul A. J.
CS Dep. Pharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO Drug Dev. Res., 13(4), 237-44
SC 1-11 (Pharmacology)
DT J
CO DDREDK
IS 0272-4391
PY 1988
LA Eng
AN CA109(25):222341v
AB A series of test compds. were studied for their ability to inhibit and block the head-twitch response to either i.p. 5-hydroxytryptophan (5-HTP) or i.v. mescaline in rats. Both responses were found to be sensitive to serotonin S2 antagonists, and there was very good agreement between the inhibitory doses in both tests, particularly for the selective serotonin S2 antagonists ritanserin and seganserin. However, these 2 compds. did not block the 5-HTP response, although they completely abolished the mescaline response. In contrast, the mixed serotonin-dopamine-norepinephrine antagonist risperidone was a potent blocker of both responses. The use of various antagonists and the combination treatments of ritanserin with haloperidol or prazosin indicated that the 5-HTP response is abolished when potent serotonin S2 antagonism is assocd.

higher doses of I (10-80 mg/kg), however, this difference disappeared, and the slopes of the dose-normalization curves became comparable for the 2 antagonists. Thus, RIS and HAL are equipotent in controlling a low level of dopaminergic overactivity by partially occupying dopamine-D2 receptors. Higher levels of functional dopamine antagonism up to satn. of the D2 receptors require a much higher dose of RIS than of HAL. Therefore, the risk of dopaminergic overblockade (and induction of extrapyramidal syndrome) is much smaller with RIS than with HAL.

IT 106266-06-2, Risperidone
(locomotor behavior from amphetamine inhibition by)

L4 ANSWER 24 OF 29 COPYRIGHT 1992 ACS
AN CA110(15):128530e
TI Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats
AU Meert, T. F.; De Haes, P.; Janssen, P. A. J.
CS Dep. Neuropsychopharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO Psychopharmacology (Berlin), 97(2), 206-12
SC 1-11 (Pharmacology)
DT J
CO PSCHDL
IS 0033-3158
PY 1989
LA Eng
AN CA110(15):128530e
AB Risperidone was studied in a 0.16 mg/kg LSD-saline drug discrimination test procedure. At doses varying from 0.0025 to 0.63 mg/kg, no LSD-like agonist effects were obsd. Risperidone was able to completely block the discriminative stimulus properties. of LSD with a min. ED50-value of 0.028 mg/kg. Risperidone was also very active over time with ref. to LSD antagonism, the ED50s after 2, 4 and 8 h pretreatment being 0.028, 0.064 and 0.44 mg/kg. Response rate redns. were only obsd. at doses .gtoreq.0.16 mg/kg after 1 h and at 0.63 mg/kg after 2 h pretreatment. At pretreatment intervals ranging between 2 and 8 h, complete antagonism of LSD without any rate effects was obtained. As compared to other LSD antagonists previously studied, risperidone was quant. better than setoperone and ritanserin and long acting than pirenperone. It was concluded that a potent central 5-HT2 and catecholamine antagonism is needed for a potent and complete antagonism of the 0.16 mg/kg LSD-cue.

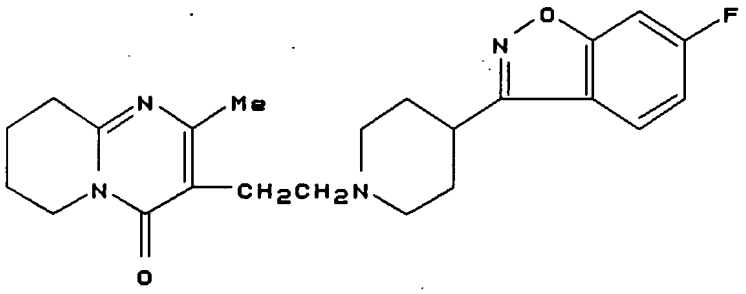
IT 106266-06-2, Risperidone
(LSD discrimination antagonism by, serotonergic receptors and catecholamines in)

L4 ANSWER 25 OF 29 COPYRIGHT 1992 ACS
AN CA110(3):18467g
TI Biochemical profile of risperidone, a new antipsychotic
AU Leysen, J. E.; Gommeren, W.; Eens, A.; De Chaffoy de Courcelles, D.; Stoof, J. C.; Jenssen, P. A. J.
CS Dep. Biochem.. Pharmaoc. Biochem., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO J. Pharmacol. Exp. Ther., 247(2), 661-70
SC 1-11 (Pharmacology)
DT J
CO JPETAB
IS 0022-3565
PY 1988
LA Eng
AN CA110(3):18467g
AB Risperidone was compared to the 5-hydroxytryptamine, antagonist

with antagonistic activity on either dopamine D2 or .alpha.1 receptors.

IT 87051-43-2 87729-89-3, Seganserin 106266-06-2
(hydroxytryptophan- and mescaline-induced head twitching response to, neurotransmitter receptors in relation to)

L4 ANSWER 27 OF 29 COPYRIGHT 1992 ACS
AN CA109(15):122371m
TI Differential effects of the new antipsychotic risperidone on large and small motor movements in rats: a comparison with haloperidol
AU Megens, A. A. H. P.; Awouters, F. H. L.; Niemegeers, C. J. E.
CS Dep. Pharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.
SO Psychopharmacology (Berlin), 95(4), 493-6
SC 1-11 (Pharmacology)
DT J
CO PSCHDL
IS 0033-3158
PY 1988
LA Eng
AN CA109(15):122371m
GI



I

AB Risperidone (I), a new antipsychotic agent, was studied for its effect on spontaneous motor activity in rats in comparison with haloperidol. Motor activity was recorded via the optical scanning technique (horizontal and vertical activity) and via a recently developed technique based on the piezo-elec. principle which, in contrast to optical scanning, is very sensitive to small, stationary movements (piezo activity). I and haloperidol at low doses depressed both vertical activity and horizontal activity. With increase of dose, the motor activity decline was faster with haloperidol than with I. Moreover, haloperidol also rapidly depressed piezo activity, whereas I depressed this component of motor behavior at much higher doses only. Visual inspection did not reveal abnormal behavioral movements following the test compds. I, therefore, preserves normal small movements over a much larger dose interval than haloperidol; this effect may be related to its relatively low cataleptogenic activity. The present results further confirm that the piezo technique may complement the optical scanning method, and thereby enhance the information on the extent that test compds. modify behavior.

IT 106266-06-2, Risperidone
(motor behavior response to, large and small movements in)

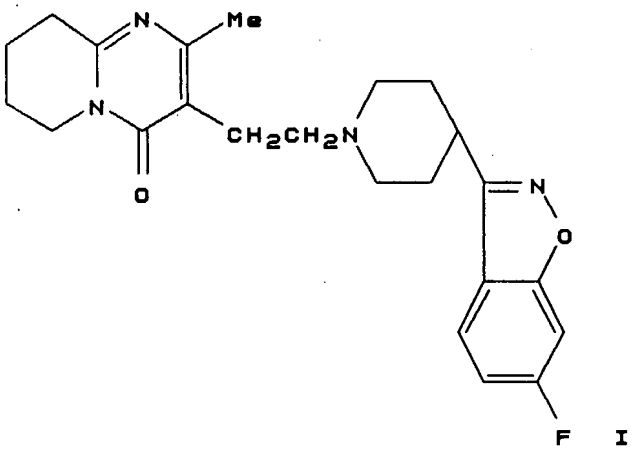
L4 ANSWER 28 OF 29 COPYRIGHT 1992 ACS
AN CA108(21):179958s
TI Pharmacology of risperidone (R 64 766), a new antipsychotic with

serotonin-S2 and dopamine-D2 antagonistic properties

AU Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F.
CS Dep. Pharmacol., Janssen Res. Found.
LO Beerse B-2340, Belg.

SO J. Pharmacol. Exp. Ther., 244(2), 685-93
SC 1-11 (Pharmacology)
SX 2
DT J
CO JPETAB
IS 0022-3565
PY 1988
LA Eng
AN CA108(21):179958s

GI



AB Comparative studies of the benzisoxazole deriv. risperidone (R 64 766) I were made with ritanserin, a selective centrally acting serotonin-S2 antagonist, and with haloperidol, a selective centrally acting dopamine-D2 antagonist. I, like ritanserin, shows activity in all tests related to serotonin-S2 antagonism, but at even lower doses (peripheral S2 antagonism at 0.0011 mg/kg, central S2 antagonism at 0.014 mg/kg). Like haloperidol, I shows activity in all tests related to dopamine-D2 antagonism; activity in rats for both compds. starts at 0.016 mg/kg, but some central nervous system-controlled functions, including the induction of catalepsy, are relatively much less affected by I. Qual., I is a mixed serotonin-dopamine antagonist. Quant., its study in dogs reveals potent dopamine-D2 antagonistic activity with excellent oral bioavailability and a relatively long duration of action. From the pharmacol. data obtained, I could be expected to possess the complementary clin. effects of a ritanserin-like serotonin-S2 and a haloperidol-like dopamine-D2 antagonist. Serotonin-S2 antagonism may improve the quality of sleep, reduce neg. and affective symptoms in schizophrenic patients, and decrease extrapyramidal symptoms induced by classical neuroleptics. Since I is a dopamine-D2 antagonist, antidelusional, antihallucinatory, and antimanic actions are expected. The 1st clin. studies indicate that 2 addnl. therapeutic targets, which are not reached with classical neuroleptics, may be obtained with I in the monotherapy of schizophrenia and related disorders: very important contact and mood-elevating properties and extrapyramidal symptoms-free maintenance therapy.

IT 106266-06-2
(antipsychotic activity and pharmacol. of, dopaminergic and serotoninergic nervous system antagonism in relation to)

L4 ANSWER 29 OF 29 COPYRIGHT 1992 ACS
AN CA106(9):67292x
TI Preparation of 1,2-benzisoxazol-3-yl and 1,2-benzisothiazol-3-yl derivatives as antipsychotics.
AU Kennis, Ludo Edmond Josephine; Vandenberk, Jan
CS Janssen Pharmaceutica N. V.
LO Belg.
SO Eur. Pat. Appl., 33 pp.
PI EP 196132 A2 1 Oct 1986
DS R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE
AI EP 86-200400 13 Mar 1986
PRAI US 85-717067 27 Mar 1985
IC ICM C07D413-14
ICS C07D417-14; C07D513-04; C07D487-04; C07D471-04; A61K031-505
ICI C07D513-04, C07D277-00, C07D239-00; C07D513-04, C07D279-00, C07D239-00; C07D487-04, C07D239-00, C07D209-00; C07D487-04, C07D239-00, C07D223-00; C07D471-04, C07D239-00
SC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT P
CO EPXXDW
PY 1986
LA Eng
AN CA106(9):67292x
GI For diagram(s), see printed CA Issue.
AB The title compds. [I; R = H, C1-6 alkyl; R1,R2 = H, halo, OH, C1-6 alkyl, alkoxy; Q = II (R3 = H, halo, C1-6 alkyl, alkoxy, etc.; R4 = H, halo; Y1,Y2 = O, S), III (R5 = H, C1-6 alkyl; A = alkylene, vinylene, etc.; Z = S, CH2, vinylene, etc.); X = O, S; n = 1-4], effective antipsychotic agents, were prepd. and incorporated into various pharmaceutical formulations. Heating a mixt. of pyrimidine salt IV.HCl 5.3, benzisoxazole V 4.4, Na2CO3 8, and KI 0.1 part in DMF at 85-90.degree. gave 46% I [R = R1 = H, R2 = 6-F, Q = III [R5 = Me, AZ = (CH2)4], X = O, n = 2]. In a selected test with rats, I showed ED50 of 0.02-0.08 .mu.g/kg s.c. against apomorphine-induced phenomena. A formulation contg. I 20, Na lauryl sulfate 6, starch 56, lactose 56, colloidal SiO2 0.8, and Mg stearate 1.2 g was made into 1000 hardened gelating capsules.
IT 106266-06-2P 106266-07-3P 106266-08-4P
106266-09-5P 106266-10-8P 106266-11-9P
106266-12-0P 106266-13-1P 106266-14-2P 106266-15-3P
106290-22-6P 106290-23-7P 108855-17-0P 108855-18-1P
(prepn. of, as antipsychotic agent)

=> fil caold; s l3
FILE 'CAOLD' ENTERED AT 15:47:41 ON 23 SEP 92
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1992 AMERICAN CHEMICAL SOCIETY (ACS)

FILE LAST UPDATED: 3 AUG 91 (910803/ED)

L5 0 L3

=> fil hom
FILE 'HOME' ENTERED AT 15:47:48 ON 23 SEP 92